IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Application No.: 10/667,216 | Examiner: Lau, Jonathan S.

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Title: **OXIDIZED HEPARIN FRACTIONS AND THEIR USE IN INHIBITING ANGIOGENESIS**

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BRIEF OF APPELLANT

This Appeal Brief, pursuant to the Notice of Appeal filed February 27, 2009, is an appeal from the rejection of the Examiner in the Office Action dated October 27, 2008.

RELATED APPEALS AND INTERFERENCES

None.

STATUS OF CLAIMS

Claims 1, 2, 5-6, 43, 49-54, 56-59, 61-63 and 91-94 are rejected. Claims 3-4, 7-42, 44-48, 55 and 60 are cancelled. Claims 64-90 are withdrawn. This Brief is in support of an appeal from the rejection of claims 1, 2, 5-6, 43, 49-54, 56-59, 61-63 and 91-94.

STATUS OF AMENDMENTS

All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

CLAIM 1 - INDEPENDENT

The present invention provides an oxidized heparin fraction having a molecular weight of from about 2,000 to about 4,000 daltons (specification, page 5, lines 18-21).

The oxidized heparin fraction is super-sulfated (specification, page 8, lines 24-27; page 6, line 28 – page 7, line 1).

The super-sulfated oxidized heparin fraction comprises an anticoagulant reduction characteristic and an angiogenesis inhibition characteristic (specification, page 7, lines 1-3)

The super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction. See specification, page 6, line 28 – page 7, line 1 ("UFH is a complex polysaccharide composed of repeating disaccharides of uronic acid → glucosamine (see Figure 1 for a sample structure of a heparin constituent). The disaccharide units may be biosynthetically modified, for example, as N-acetyl or N-sulfate glucosamine, 2-O-sulfate uronic acid and 6-O-sulfate and/or 3-O-sulfate glucosamine").

The super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis. See specification, page 29, Table 3 (shows that the FGF2 + super-sulphated oxidized ultra-LMWH reduces the FGF2-stimulated number of vessel branch points in a circular region equal to the area of a FGF2-saturated filter disk from 264 to 90 ± 8

which is at the level of the control (PBS) of 95 ± 11, so that the FGF2 + super-sulphated oxidized ultra-LMWH fully inhibits FGF2 induced angiogenesis).

CLAIM 2 – DEPENDENT

The present invention provides the oxidized heparin fraction of claim 93, wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic (specification, page 25, line 13: Table 1, super-sulfated oxidized heparin fraction vs. heparin at concentration of 1.0 μg).

CLAIM 5 – DEPENDENT

The present invention provides the oxidized heparin fraction of claim 93, wherein the anticoagulant reduction characteristic comprises the second anticoagulant reduction characteristic (specification, page 27, line 4: Table 2, super-sulfated oxidized heparin fraction vs. heparin at concentration of 1.0 μg).

CLAIM 6 – DEPENDENT

The present invention provides the oxidized heparin fraction of claim 93, wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic and the second anticoagulant reduction characteristic (specification, page 25, line 13: Table 1, super-sulfated oxidized heparin fraction vs. heparin at concentration of 1.0 μg; specification, page 27, line 4: Table 2, super-sulfated oxidized heparin fraction vs. heparin at concentration of 1.0 μg).

CLAIM 43 – DEPENDENT

The present invention provides a composition comprising from about 60% to about 100% of the oxidized heparin fraction of claim 1, and from about 0% to about 40% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan sulfates, heparin derivatives, or combinations thereof (specification, page 20, lines 26-32).

CLAIM 49 – DEPENDENT

The present invention provides the composition of claim 43, further comprising a non-heparin anticoagulant (specification, page 17, lines 14-15).

CLAIM 50 – DEPENDENT

The present invention provides the composition of claim 49, wherein the non-heparin anticoagulant is selected from the group consisting of anti-Xa compounds, anti-IIa compounds, anti-tissue factor compounds, anti-VIIa compounds, and combinations thereof (specification, page 17, lines 14-17).

CLAIM 51 – DEPENDENT

The present invention provides the composition of claim 43, further comprising a non-heparin angiogenic inhibitor (specification, page 16, lines 14-15).

CLAIM 52 – DEPENDENT

The present invention provides the composition of claim 51, wherein the non-heparin angiogenic inhibitor is selected from the group consisting of integrin inhibitory compounds, angiostatin, endostatin, fibroblast growth factor inhibitors, fibroblast growth factor receptor inhibitors, vascular endothelial growth factor inhibitors, thrombospondin, platelet factor 4, interferon, interleukin 12, thalidomide, and combinations thereof (specification, page 16, lines 15-26).

CLAIM 53– DEPENDENT

The present invention provides the composition of claim 43, further comprising a cytotoxic or chemotherapeutic agent (specification, page 20, lines 11-15).

CLAIM 54– DEPENDENT

The present invention provides the composition of claim 53, wherein the cytotoxic or chemotherapeutic agent is selected from the group consisting of nitrogen mustard, aziridine thiotepa, alkyl sulfonate, nitrosoureas, platinum complexes, non-classic alkylators, substituted urea, antitumor antibiotics, microtubule agents, and asparaginase (specification, page 20, lines 21-25).

CLAIM 56 – DEPENDENT

The present invention provides a polymeric structure comprising the oxidized heparin fraction of claim 1, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or copolymerization, non-covalently incorporated into a

matrix of the polymeric structure, or encapsulated as a biomedical material within the polymeric structure (specification, page 15, line 25 – page 16, line 6).

CLAIM 57 – DEPENDENT

The present invention provides the polymeric structure of claim 56, wherein said oxidized heparin fraction is non-covalently incorporated into the matrix (specification, page 15, lines 29-30).

CLAIM 58 – DEPENDENT

The present invention provides the polymeric structure of claim 57, wherein the matrix comprises a biocompatible polymer and provides for a sustained release of said oxidized heparin fraction (specification, page 15, lines 25-28).

CLAIM 59 – DEPENDENT

The present invention provides the polymeric structure of claim 58, wherein said biocompatible polymer is ethylene vinyl acetate (specification, page 15, lines 25-28).

CLAIM 61 – DEPENDENT

The present invention provides the polymeric structure of claim 56, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting (specification, page 15, lines 29-30).

CLAIM 62 – DEPENDENT

The present invention provides the polymeric structure of claim 56, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by copolymerization (specification, page 15, lines 29-30).

CLAIM 63 – DEPENDENT

The present invention provides the polymeric structure of claim 56, wherein said oxidized heparin fraction is encapsulated as said biomedical material within the polymeric structure (specification, page 16, lines 2-6).

CLAIM 91 – DEPENDENT

The present invention provides the oxidized heparin fraction of claim 1, wherein the super-sulfated oxidized heparin fraction comprises a sulfate to carboxylate ratio of about 5:1. (specification, page 9, lines 23-25).

CLAIM 92 – DEPENDENT

The present invention provides the oxidized heparin fraction of claim 1, wherein from about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction (specification, page 9, lines 25-28).

CLAIM 93 – DEPENDENT

The present invention provides the oxidized heparin fraction of claim 1,

wherein the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof;

wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood (specification, page 25, line 13: Table 1, super-sulfated oxidized heparin fraction vs. heparin at concentration of 1.0 μg);

wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT) (specification, page 27, line 4: Table 2, super-sulfated oxidized heparin fraction vs. heparin at concentration of 1.0 μg); and

wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the

EC growth medium (specification, page 29, line 2: Table 3, super-sulfated oxidized heparin fraction vs. FGF2 at concentration of 1.0 μg).

CLAIM 94 – DEPENDENT

The present invention provides a method, comprising forming the oxidized heparin fraction of claim 1, wherein said forming the oxidized heparin fraction comprises O-sulfating the first oxidized heparin fraction by performing sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction. See specification, page 6, line 28 – page 7, line 1 ("UFH is a complex polysaccharide composed of repeating disaccharides of uronic acid → glucosamine (see Figure 1 for a sample structure of a heparin constituent). The disaccharide units may be biosynthetically modified, for example, as N-acetyl or N-sulfate glucosamine, 2-O-sulfate uronic acid and 6-O-sulfate and/or 3-O-sulfate glucosamine").

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

2. Claims 1, 2, 5, 6, 43 and 91-94 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892).

3. Claims 1, 43, 49 and 50 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Weitz et al. (US Patent 6,075,013, issued 13 Jun 2000, of record).

4. Claims 1 and 56-59 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, cited in PTO-892).

5. Claims 1, 43 and 51-54 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, cited in PTO-892) as applied to claims 1 and 56-59 above, and further in view of Kerbel et al. (Cancer and Metastasis Reviews, 2001, 20, p79-86, cited in PTO-892).

6. Claims 1, 56, 61 and 62 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Scholander (US Patent 6,461,665, issued 08 Oct 2002, of record).

ARGUMENT

GROUND OF REJECTION 1

Claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Claim 1

The Examiner argues that in order to satisfy the written description requirement, a chemical genus must be defined by a chemical structure, chemical formula, or a chemical name, which is alleged by the Examiner to not be satisfied for the claimed super-sulfated oxidized heparin fraction recited in claim 1.

In response, Appellant asserts that the preceding argument by the Examiner is not based on the latest case law and thus does not fully and accurately express the current law regarding how a patent application may satisfy the written description requirement with respect to a genus.

Appellant cites *In re Alonso*, USPTO 2008-1079 (Fed. Cir. October 30, 2008) as being the ***latest decision*** by the Federal Circuit how a patent application may satisfy the written description requirement with respect to a genus. The *Alonso* court asserted that there are several alternatives for satisfying the written description requirement in describing a genus; i.e. by "disclosing (1) a representative number of species in that genus; or (2) its "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.""

Appellant next presents three alternative modalities by which the super-sulfated oxidized heparin fraction recited in claim 1 is in conformity with the written description requirement according to *In re Alonso*, namely: (1) by identifying complete or partial structure; (2) by disclosing a representative number of species; or (3) identifying functional characteristics when coupled with a known or disclosed correlation between function and structure.

Identifying Complete or Partial Structure

If the structural of "oxidized heparin fraction" is clear, then the structure of "super-sulfated oxidized heparin fraction" is also clear, because claim 1 recites: "the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction".

Next, Appellant demonstrates that the specification adequately describes the structure of "oxidized heparin fraction".

The specification describes a heparin fraction as a fragment of heparin (derived from fragmentation of heparin) having a molecular weight of from about 2,000 to about 4,000 daltons (specification, page 5, line 28 – page 6, line 5) and that a heparin fraction may be oxidized to form an oxidized heparin fraction (specification, page 5, lines 7-10).

The United States Patent and Trademark Office recognizes that "heparin" is known and unambiguous, as evidenced by the fact that on May 25, 2009, Appellant's Representative did a search of the USPTO patent database and found "heparin" to appear in the claims of 2848 issued

patents wherein "heparin" is not defined in almost all of these issued patents. Therefore, the meaning of "heparin", which includes its structure, is not an issue.

Given heparin, the structure of a heparin fraction is defined in the specification, specification, page 5, line 28 – page 6, line 5 as a fragment of heparin (derived from fragmentation of heparin) having a molecular weight of from about 2,000 to about 4,000 daltons, which is clear. For further clarification, the specification, page 6, line 28 – page 7, line 21 presents details as to how heparin may be fractionated in practice.

Given a heparin fraction, an oxidized heparin fraction is a heparin fraction that has been oxidized (specification, page 5, lines 7-10). For further clarification, the specification, page 7, lines 3 - 21 presents detail as to how heparin fractions may be oxidized in practice

The United States Patent and Trademark Office recognizes that the meaning of "oxidized" is known and unambiguous, as evidenced by the fact that on May 25, 2009, Appellant's Representative did a search of the USPTO patent database and found "oxidized" to appear in the claims of 13,545 issued patents wherein "oxidized" is not defined in almost all of these issued patents. Therefore, the meaning of "oxidized" is not an issue. Accordingly, the structure of oxidized heparin fraction is adequately described in the specification.

In summary, the structure of "super-sulfated oxidized heparin fraction" is adequately described in the specification, because; (1) "oxidized heparin fraction" is adequately described in the specification as discussed *supra*; and (2) language of claim 1 ("the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction") describes the structure of super-sulfated

oxidized heparin fraction in terms of a well-defined sulfate substitution applied to an oxidized heparin fraction.

Accordingly, the specification satisfies the written description requirement for "super-sulfated oxidized heparin fraction" by identifying a complete or partial structure of the super-sulfated oxidized heparin fraction.

Disclosing a Representative Number of Species

The specification, page 6, line 28 – page 7, line 1 discloses a multiplicity of sulfation sites by reciting: "UFH is a complex polysaccharide composed of repeating disaccharides of uronic acid → glucosamine (see Figure 1 for a sample structure of a heparin constituent). The disaccharide units may be biosynthetically modified, for example, as N-acetyl or N-sulfate glucosamine, 2-O-sulfate uronic acid and 6-O-sulfate and/or 3-O-sulfate glucosamine.", which supports the claimed "the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction".

Accordingly, the specification satisfies the written description requirement for "super-sulfated oxidized heparin fraction" by identifying a representative number of species.

Identifying Functional Characteristics When Coupled With a Known or Disclosed Correlation Between Function and Structure

Tables 1 and 2 on pages 25 and 27, respectively, of the specification describe correlation between function and structure of super-sulfated heparin fraction with respect to anticoagulant reduction functionality.

Table 1 shows maximal anticoagulant reduction (96-100% inhibition of clotting) activity with heparin or the LMWH dalteparin at a concentration of 1.0 μg, while the oxidized ultra-LMWH or super-sulfated oxidized ultra-LMWH showed no significant anticoagulant activity at the same concentration of 1.0 μg.

Table 2: further support the data in Table 1 by using different means of measuring clotting, including APTT or PT, where maximal increase in APTT values were shown with LMWH dalteparin or standard heparin at 1.0 μg with no change in APTT with either oxidized or super-sulfated oxidized LMWH heparin.

Thus for anticoagulant reduction functionality, Tables 1 and 2 clearly differentiate super-sulfated oxidized heparin fractions from both LMWH dalteparin and standard heparin, but do not differentiate between sulfated oxidized heparin fractions and oxidized heparin fractions. However, the preceding findings in Tables 1 and 2 may be combined with the differentiation between sulfated oxidized heparin fractions and oxidized heparin fractions by the following language recited in claim 1: "the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction". Use of the preceding combination (i.e., Tables 1 and 2 combined with the preceding recited language in claim 1) to satisfy the written description requirement is in accord with *In re Alonso*.

Tables 3 and 6 on pages 29 and 33, respectively, of the specification describe correlation between function and structure of super-sulfated heparin fraction with respect to angiogenesis inhibition functionality.

Table 3 shows that oxidized super sulfated ultra-LMWH fully reverses endothelial tube formation (angiogenesis) back to the un-stimulated control state more effectively as compared with oxidized ultra-LMWH at 1.0 μg concentration, both of which being more effective than the standard LMWH dalteparin at 10 fold higher concentration (10.0 μg).

Table 6 demonstrates a greater potency of LWMH super-sulfated oxidized heparin species (2,000-4,000 daltons) as compared with LWMH oxidized heparin species (2,000-4,000 daltons) or LMWH tinzaparin or enoxaparin at 1.0 μg in releasing the endogenous mediator for the inhibition of angiogenesis from human endothelial cells namely issue factor pathway inhibitor (TFPI).

Accordingly, the specification satisfies the written description requirement under 35 U.S.C. § 112, first paragraph for "super-sulfated oxidized heparin fraction" by identifying functional characteristics when coupled with a known or disclosed correlation between function and structure with respect to anticoagulant reduction functionality and angiogenesis inhibition functionality.

Based on the preceding arguments, Appellant respectfully requests that the rejection of claim 1 with respect to the written description requirement under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94

Appellant has argued *supra* that the specification satisfies the written description requirement under 35 U.S.C. § 112, first paragraph for the super-sulfated oxidized heparin fraction recited in claim 1. Since claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 depend from claim 1, Appellant asserts that claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 likewise satisfies the written description requirement under 35 U.S.C. § 112, first paragraph for the super-sulfated oxidized heparin fraction.

The Examiner alleges that claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 include functional language that cannot be used for satisfying the written description requirement with respect to a chemical genus being claimed. However, the chemical genus being claimed in claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 is super-sulfated oxidized heparin fraction of claim 1 which satisfies the written description requirement under 35 U.S.C. § 112, first paragraph, as explained *supra*. Appellant does not rely on functional language or other limitations in claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 to satisfy the written description requirement for the chemical genus of super-sulfated oxidized heparin fraction.

Appellant notes that claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 have not been rejected under 35 U.S.C. § 112, first paragraph outside the context of defining the chemical genus. Nonetheless, Appellant asserts that the functional language and other limitations in

claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94, taken outside the context of defining the chemical genus, are analogous to limitations that typically appear in issued patents and are not in violation of the written description requirement under 35 U.S.C. § 112, first paragraph.

Based on the preceding arguments, Appellant respectfully requests that the rejection of claims 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 with respect to the written description requirement under 35 U.S.C. § 112, first paragraph be withdrawn.

GROUND OF REJECTION 2

Claims 1, 2, 5, 6, 43 and 91-94 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892).

Appellant respectfully contends that Naggi does not anticipate claim 1, because Naggi does not teach each and every feature of claim 1.

As a first example of why Naggi does not anticipate claim 1, Naggi does not teach the feature: "wherein the super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis".

Although Naggi teaches supersulfated heparins, Naggi's technique for generating the supersulfated heparins differs from Appellant's technique of generating the claimed super-sulfated oxidized heparin fractions. Specifically, Naggi teaches generating supersulfated heparins by a process of treating heparin with a mixture of sulfuric acid and chlorosulfonic acid (see Naggi, col. 4, lines 66-67), which markedly differs from Appellant's described process of O-sulfating a first oxidized heparin fraction (via sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction).

Therefore, it cannot be argued that any of Naggi's supersulfated heparins are the same as any of Appellant's super-sulfated oxidized heparin fractions that were demonstrated in Table 3 on page 29 of Appellant's specification as having the characteristic of fully inhibiting FGF2 induced angiogenesis. The scope of claim 1 does not include all super-sulfated oxidized heparin fractions that may potentially exist, but is specifically limited to those super-sulfated oxidized heparin fractions that fully inhibit FGF2 induced angiogenesis.

Appellant asserts that it cannot be argued that Naggi's supersulfated heparins fully inhibit FGF2 induced angiogenesis in the absence of proof by experimental or test results. Since such experimental or test results do not exist in Naggi, and since Naggi does not explicitly teach that that Naggi's supersulfated heparins fully inhibit FGF2 induced angiogenesis, Appellant maintains that Naggi does not teach the preceding feature of claim 1.

As evidence that Naggi did not teach fully inhibiting FGF2 induced angiogenesis though use of supersulfaction, Appellant cites Lars Lundin et al., Selectively Desulfated Heparin Inhibits Fibroblast Growth Factor-induced Mitogenicity and Angiogenesis, Journal of Biological Chemistry, Vol. 275, No. 32 (August 11, 2000), (hereinafter, "Lundin"), a copy of which was included in Appendix A of Appellant's office action response filed December 31, 2007. See Lundin's Abstract ("FGF-2 induced angiogenesis in chick embryos was inhibited by 6-O-desulfated heparein"). In contrast, Appellant is claiming sulfation of an oxygenated heparin fraction to inhibit FGF2 induced angiogenesis, which is the exact opposite of desulfation. In light of Lundin's teaching of desulfation for inhibiting angiogenesis which teaches the state of the art in year 2000 well after the date of 1988 when the Naggi patent was issued, it is clear that Naggi did not teach fully inhibiting FGF2 induced angiogenesis though use of supersulfaction. In light of Lundin's teaching of desulfation for inhibiting angiogenesis, Appellant asserts that Appellant's teaching that sulfation of an oxygenated heparin fraction (in the manner described in Appellant's specification and claimed in claim 1) totally inhibits FGF2 induced angiogenesis is an ***unexpected result*** that was not taught by Naggi in 1988.

In addition, the preceding feature of claim 1 distinguishes Naggi as follows. Appellant's specification in Paragraph [0005] beginning on page 2, line 16 states that it is known in the art

that FGF2 induced angiogenesis plays a role in pathological angiogenesis associated with solid tumors, diabetic retinopathy, and rheumatoid arthritis. Therefore, the capability of full inhibition of FGF2 induced angiogenesis by the super-sulphated oxidized ultra-LMWH of the present invention may be beneficially employed to inhibit accelerated angiogenesis for cancer cases in which a tumor secrets excess angiogenesis growth factors including FGF2, and also to inhibit angiogenesis associated with diabetic retinopathy and rheumatoid arthritis in which FGF2 is implicated, without affecting basal angiogenesis (i.e., normal or physiological angiogenesis) as characterized by the PBS control of Tables 3 and 4 on pages 29 and 30, respectively, of Appellant's specification as discussed *supra*. In contrast, Naggi is totally silent as to FGF2 induced angiogenesis and is totally silent as to the use of supersulfated heparind for treatment of cancer, diabetic retinopathy and rheumatoid arthritis, which is additional evidence that Appellant's super-sulfated oxidized heparin fraction is patentably distinct from Naggi's supersulfated heparins.

As a second example of why Naggi does not anticipate claim 1, Naggi does not teach the feature: "wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction".

The Examiner incorrectly argues that the preceding feature of claim 1 is a product-by-process limitation. Appellant asserts the preceding feature of claim 1 does not recite how the super-sulfated oxidized heparin fraction of claim 1 is actually produced. Rather, the preceding feature of claim 1 recites "wherein the super-sulfated oxidized heparin fraction has a chemical

structure of ..." for the purpose of describing the chemical structure of the claimed super-sulfated oxidized heparin fraction.

Naggi would teach the preceding feature of claim 1 if the supersulfated heparins resulting from Naggi's process for generating supersulfated heparins have the same chemical structure as would result from implementing the process in claim 1 of O-sulfating a first oxidized heparin fraction (via sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction. However, Naggi does not teach the preceding feature of claim, because Naggi does not teach that Naggi's process for generating sursulfated heparins has the same chemical structure as would result from implementing the process in claim 1 of O-sulfating a first oxidized heparin fraction (via sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction). Therefore, the Examiner has not persuasively argued that Naggi's process of treating heparin with a mixture of sulfuric acid and chlorosulfonic acid generates the super-sulfated oxidized heparin of claim 1.

The Examiner argues that the chemical structure shown in Naggi, col. 6, lines 1-12, with m=4 and A=SO_3^- satisfies the preceding feature of claim 1.

In response, Appellant asserts that claim 1 requires the super-sulfated oxidized heparin fraction to have a chemical structure obtained by O-sulfating a first oxidized heparin fraction (via sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction). However, Naggi teaches generating supersulfated heparins by a process of treating heparin with a mixture of sulfuric acid and chlorosulfonic acid (see Naggi, col. 4, lines 66-67), which markedly differs from the preceding process recited in claim 1. Naggi does not teach that

Naggi's process of treating heparin with a mixture of sulfuric acid and chlorosulfonic acid generates super-sulfated heparins that have a chemical structure obtained by O-sulfating a first oxidized heparin fraction (via sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction). Therefore, the Examiner has not persuasively argued that Naggi's process of treating heparin with a mixture of sulfuric acid and chlorosulfonic acid generates the super-sulfated oxidized heparin of claim 1.

Thus it cannot be argued that the chemical structure shown in Naggi, col. 6, lines 1-12, with m=4 and A=SO_3^- is a chemical structure that would result from implementing the process in claim 1 of O-sulfating a first oxidized heparin fraction (via sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction).

I n "Response to Applicant's Remarks", the Examiner argues: "Naggi et al. discloses the heparin treated with sulfuric acid and chlorosulfonic acid, a strong oxidizing agent, to depolymerize and super-sulfate heparin (example 12 at column 12, lines 1-30), which necessarily encompasses the reaction sequence comprising the steps of oxidizing said heparin in order to depolymerize said heparin and then performing sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin to produce the super-sulfated heparin of formula IV, meeting the instant limitations of instant claim 94. Naggi et al. discloses that it is well known in the art that the process of depolymerizing heparin, such as by oxidation using acid and a strong oxidizing agent such as hydrogen peroxide (column 4, lines 10-20), occurs prior to sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin, and it is the invention of Naggi et al. to perform sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin (column 5, lines 5-30). Therefore

the existence of the first oxidized fraction prior to 0-sulfation is implicitly present as a reaction intermediate in the process disclosed by Naggi et al."

In response, Appellant asserts that the preceding description by the Examiner of chemical detail, including intermediate processes, that allegedly occur for EXAMPLE 2 in Naggi, col. 12, lines 1-30 is not disclosed in Naggi. The Examiner has not submitted evidence allegedly demonstrating that the preceding description by the Examiner is correct, especially with regard to intermediate structures produced from treating heparin with sulfuric acid and chlorosulfonic acid.

Based on the preceding arguments, Appellant respectfully maintains that Naggi does not anticipate claim 1, and that claim 1 is in condition for allowance.

Claim 93

Since claim 93 depend from claims 1, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 93 is likewise not anticipated by Naggi.

In addition with respect to claims 93, Naggi does not teach the feature:

"wherein the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof; wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood; wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood

by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT); and wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium".

The Examiner argues: "Naggi et al. discloses the reduction of the anticoagulation reduction characteristic with regards to the activated partial thromboplastin time (APTT) (column 9, lines 7-11 and 47-60), explicitly meeting the limitations of instant claims 5 and 93... The depolymerized and supersulfated heparin disclosed by Naggi et al. shows a reduction of the APTT or Anti-Xa as measured in terms of units/mL in table I (column 9, lines 50-65) for products AH-17 and AH-19, relative to the heparin D-212, the reduction being approximately 76.5% (0.05 U/ml / 0.212 U/ml) for the same dose (50 IU/kg), or a reduced prolongation of clotting time of human blood by at least 75% relative to the prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)."

In response, Appellant notes that the data in the APTT column in TABLE 1 of Naggi, col. 9, lines 50-59 ***is not expressed in units of clotting time*** (or prolongation of clotting time) as

is recited in claims 5 and 93, but rather ***is expressed in units of U/ml*** which is totally irrelevant to the preceding feature of claims 5 and 93. Naggi does not present any data that teaches the limitation in claims 5 and 93 of: "wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces ***a prolongation of clotting time*** of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)" (emphasis added).

In addition with respect to claim 93, Naggi teaches the feature: "wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium".

The Examiner makes the allegation that Naggi inherently teaches the preceding feature of claim 93, but does not provide evidence to support the preceding allegation.

Accordingly, Appellant respectfully maintains that Naggi does not anticipate claim 93.

Claim 2

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Since claim 2 depends from claims 93, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 2 is likewise not anticipated by Naggi.

In addition with respect to claims 2, Naggi does not teach the feature: "wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic" . Appellant notes (from claim 93) that "the first anticoagulant reduction characteristic (from claim 93) is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood".

The Examiner argues: "Naggi et al. is silent as to an angiogenesis inhibition characteristic and the anticoagulant reduction characteristic in terms of a "percent inhibition of platelet clot strength," but does recite that the depolymerized and supersulfated heparin shows a weak anticoagulant activity (column 5, lines 41-45), providing evidence tending to show inherency when combined with said activity measured with regard to APTT and Anti-Xa. Therefore it is apparent from what is disclosed that the functional characteristics recited in instant claims 2 and 6 are inherent in the compound disclosed by Naggi et al."

In response, Appellant respectfully contends that the Examiner's argument that Naggi recites that the depolymerized and supersulfated heparin shows a weak anticoagulant activity does not inherently teach the feature of "wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in

human blood being equal to the concentration of the unfractionated heparin in human blood". Appellant respectfully asserts that it cannot be concluded that the recited reduction of a mean percent inhibition of platelet clot strength by factor of at least about 8 is inherently taught by the existence of a weak anticoagulant activity.

In further response, Appellant asserts that Naggi does not disclose the same super-sulfated oxidized heparin fraction as is claimed in claim 1, as explained *supra* in conjunction with claim 1. Therefore, the Examiner's allegation that Naggi's supersulfated heparin inherently comprises the first anticoagulant reduction characteristic is not persuasive.

Furthermore, even if some species of Naggi's supersulfated heparin are within the scope of the super-sulfated oxidized heparin fraction of claim 1, the scope of claim 2 includes only those super-sulfated oxidized heparin fractions that comprise the first anticoagulant reduction characteristic, and Naggi does not teach any species of supersulfated heparin that comprises the first anticoagulant reduction characteristic.

Accordingly, Appellant respectfully maintains that Naggi does not anticipate claim 2.

Claim 5

Since claim 5 depends from claims 93, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 5 is likewise not anticipated by Naggi.

In addition with respect to claims 5, Naggi does not teach the feature: "wherein the anticoagulant reduction characteristic comprises the second anticoagulant reduction characteristic". Appellant notes (from claim 93) that "the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of

human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)".

The Examiner argued, in conjunction with claim 93, that Naggi, col. 9, lines 7-11 and 47-60 teaches the preceding feature of claim 5.

In response, Appellant notes that the data in the APTT column in TABLE 1 of Naggi, col. 9, lines 50-59 ***is not expressed in units of clotting time*** (or prolongation of clotting time) as is recited in claims 5 and 93, but rather ***is expressed in units of U/ml*** which is totally irrelevant to the preceding feature of claims 5 and 93. Naggi does not present any data that teaches the limitation in claims 5 and 93 of: "wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces ***a prolongation of clotting time*** of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)" (emphasis added).

Accordingly, Appellant respectfully maintains that Naggi does not anticipate claim 5.

Claim 6

Since claim 6 depends from claims 93, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 6 is likewise not anticipated by Naggi.

In addition with respect to claims 6, Naggi does not teach the feature: "wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic and the second anticoagulant reduction characteristic".

Appellant notes (from claim 93) that "the first anticoagulant reduction characteristic (from claim 93) is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood".

With respect to the first anticoagulant reduction characteristic, the Examiner argues: "Naggi et al. is silent as to an angiogenesis inhibition characteristic and the anticoagulant reduction characteristic in terms of a "percent inhibition of platelet clot strength," but does recite that the depolymerized and supersulfated heparin shows a weak anticoagulant activity (column 5, lines 41-45), providing evidence tending to show inherency when combined with said activity measured with regard to APTT and Anti-Xa. Therefore it is apparent from what is disclosed that the functional characteristics recited in instant claims 2 and 6 are inherent in the compound disclosed by Naggi et al."

In response, Appellant respectfully contends that the Examiner's argument that Naggi recites that the depolymerized and supersulfated heparin shows a weak anticoagulant activity

does not inherently teach the feature of "wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood". Appellant respectfully asserts that it cannot be concluded that the recited reduction of a mean percent inhibition of platelet clot strength by factor of at least about 8 is inherently taught by the existence of a weak anticoagulant activity.

In further response, Appellant asserts that Naggi does not disclose the same super-sulfated oxidized heparin fraction as is claimed in claim 1, as explained *supra* in conjunction with claim 1. Therefore, the Examiner's allegation that Naggi's supersulfated heparin inherently comprises the first anticoagulant reduction characteristic is not persuasive.

Furthermore, even if some species of Naggi's supersulfated heparin are within the scope of the super-sulfated oxidized heparin fraction of claim 1, the scope of claim 2 includes only those super-sulfated oxidized heparin fractions that comprise the first anticoagulant reduction characteristic, and Naggi does not teach any species of supersulfated heparin that comprises the first anticoagulant reduction characteristic.

Appellant notes (from claim 93) that "the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being

equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)".

The Examiner argued, in conjunction with claim 93, that Naggi, col. 9, lines 7-11 and 47-60 teaches the second anticoagulant reduction characteristic of claim 6.

In response, Appellant notes that the data in the APTT column in TABLE 1 of Naggi, col. 9, lines 50-59 ***is not expressed in units of clotting time*** (or prolongation of clotting time) as is recited in claims 5 and 93, but rather ***is expressed in units of U/ml*** which is totally irrelevant to the preceding feature of claims 5 and 93. Naggi does not present any data that teaches the limitation in claims 5 and 93 of: "wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces ***a prolongation of clotting time*** of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT)" (emphasis added).

Accordingly, Appellant respectfully maintains that Naggi does not anticipate claim 6.

Claim 91

Since claim 91 depends from claims 1, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 91 is likewise not anticipated by Naggi.

In addition with respect to claim 91, Naggi does not teach the feature: "wherein the super-sulfated oxidized heparin fraction comprises a sulfate to carboxylate ratio of about 5:1".

The Examiner argues: "Naggi et at. discloses a preferred embodiment of depolymerized and supersulfated heparin wherein the molecular weight is 3000-5000 and the sulfation degree is 2.6 (example 12 at column 12, lines 1-30), or a heparin fraction wherein 52% of the primary and secondary hydroxyl groups are substituted by 0-sulfate esters, meeting limitations of instant claim 1, 2, 5, 6, 91-93. The term "sulfate to carboxylate ratio of about 5:1" in instant claim 91 broadens the ratio without guidance as to the range encompassed by the term "about", and the disclosed sulfation degree of 2.6, or ratio of sulfate to carboxylate of 2.6:1, is interpreted to be about 5:1 because it is the same order of magnitude"

In response, Appellant does not agree that 2.6 is about 5:1, because 5:1 is more than 90% higher than 2.6.

Accordingly, Appellant respectfully maintains that Naggi does not anticipate claim 91.

Claim 92

Since claim 92 depends from claim 1, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 21 is likewise not anticipated by Naggi

In addition with respect to claim 92, Naggi does not teach the feature: "wherein from about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction"

The Examiner does not even allege that Naggi teaches the preceding feature of claim 92

Accordingly, Appellant respectfully maintains that Naggi does not anticipate claim 92.

Claim 94

Since claim 94 depends from claim 1, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 94 is likewise not anticipated by Naggi

In addition with respect to claim 94, Naggi does not teach the feature: "forming the oxidized heparin fraction of claim 1, wherein said forming the oxidized heparin fraction comprises O-sulfating the first oxidized heparin fraction by performing sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction".

I n "Response to Applicant's Remarks", the Examiner argues: "Naggi et al. discloses the heparin treated with sulfuric acid and chlorosulfonic acid, a strong oxidizing agent, to depolymerize and super-sulfate heparin (example 12 at column 12, lines 1-30), which necessarily encompasses the reaction sequence comprising the steps of oxidizing said heparin in order to depolymerize said heparin and then performing sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin to produce the super-sulfated heparin of formula IV, meeting the instant limitations of instant claim 94. Naggi et al. discloses that it is well known in the art that the process of depolymerizing heparin, such as by oxidation using acid and a strong oxidizing agent such as hydrogen peroxide (column 4, lines 10-20), occurs prior to sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin, and it is the invention of Naggi et al. to perform sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin (column 5, lines 5-30). Therefore

the existence of the first oxidized fraction prior to 0-sulfation is implicitly present as a reaction intermediate in the process disclosed by Naggi et al."

In response, Appellant asserts that the preceding description by the Examiner of chemical detail, including intermediate processes, that allegedly occur for EXAMPLE 2 in Naggi, col. 12, lines 1-30 is not disclosed in Naggi. The Examiner has not submitted evidence allegedly demonstrating that the preceding description by the Examiner is correct, especially with regard to intermediate structures produced from treating heparin with sulfuric acid and chlorosulfonic acid.

Accordingly, Naggi does not anticipate claim 94.

Claim 43

Since claim 43 depends from claim 1, which Appellant has argued *supra* to not anticipated by Naggi, Appellant maintains that claim 43 is likewise not anticipated by Naggi

In addition with respect to claim 43, Naggi does not teach the feature: "A composition comprising from about 60% to about 100% of the oxidized heparin fraction of claim 1 ...".

The Examiner argues: "Naggi et al. discloses the compound in the form of a pharmaceutical composition (column 10, lines 55-57), or a composition comprising about 100% of the depolymerized and supersulfated heparin ... ".

In response, Appellant respectfully contends that the preceding citation by the Examiner to Naggi, col. 10, lines 55-57 which recites "pharmaceutical compositions containing, as active ingredient, a depolymerized and supersulfated heparin of formula IV above" does not teach a "composition comprising from about 60% to about 100% of the oxidized heparin fraction".

Therefore, Naggi does not anticipate claim 43.

GROUND OF REJECTION 3

Claims 1, 43, 49 and 50 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Weitz et al. (US Patent 6,075,013, issued 13 Jun 2000, of record).

Claim 1

With respect to claim 1, the Examiner has not invoked Weitz as a reference as allegedly disclosing any feature specific to claim 1. The Examiner appears to rely on Naggi as allegedly disclosing all of the features of claim 1 based on the Examiner's prior arguments with respect to Naggi allegedly anticipating claim 1.

In response, Appellant relies on Appellant's arguments *supra* as to why Naggi does not teach or suggest all of the features of claim 1.

Accordingly, Appellant maintains that claim 1 and is not unpatentable over Naggi in view of Weitz.

Claim 43

With respect to claim 43, the Examiner has not invoked Weitz as a reference as allegedly disclosing any feature specific to claim 43. The Examiner appears to rely on Naggi as allegedly disclosing all of the features of claim 43 based on the Examiner's prior arguments with respect to Naggi allegedly anticipating claim 43.

In response, Appellant relies on Appellant's arguments *supra* as to why Naggi does not teach or suggest all of the features of claim 43.

Accordingly, Appellant maintains that claim 43 and is not unpatentable over Naggi in view of Weitz.

Claim 49

Since claim 49 depends from claim 43, which Appellant has argued *supra* to not unpatentable over Naggi in view of Weitz, Appellant maintains that claim 49 is likewise not unpatentable over Naggi in view of Weitz.

Claim 50

Since claim 50 depends from claim 43, which Appellant has argued *supra* to not unpatentable over Naggi in view of Weitz, Appellant maintains that claim 50 is likewise not unpatentable over Naggi in view of Weitz.

GROUND OF REJECTION 4

Claims 1 and 56-59 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, cited in PTO-892).

Claim 1

With respect to claim 1, the Examiner has not invoked Conrad as a reference as allegedly disclosing any feature specific to claim 1. The Examiner appears to rely on Naggi as allegedly disclosing all of the features of claim 1 based on the Examiner's prior arguments with respect to Naggi allegedly anticipating claim 1.

In response, Appellant relies on Appellant's arguments *supra* as to why Naggi does not teach or suggest all of the features of claim 1.

Accordingly, Appellant maintains that claim 1 and is not unpatentable over Naggi in view of Conrad.

Claim 56

Since claim 56 depends from claim 1, which Appellant has argued *supra* to not unpatentable over Naggi in view of Conrad, Appellant maintains that claim 56 is likewise not unpatentable over Naggi in view of Conrad.

Claim 57

Since claim 57 depends from claim 1, which Appellant has argued *supra* to not

unpatentable over Naggi in view of Conrad, Appellant maintains that claim 57 is likewise not unpatentable over Naggi in view of Conrad.

Claim 58

Since claim 58 depends from claim 1, which Appellant has argued *supra* to not unpatentable over Naggi in view of Conrad, Appellant maintains that claim 58 is likewise not unpatentable over Naggi in view of Conrad.

Claim 59

Since claim 59 depends from claim 1, which Appellant has argued *supra* to not unpatentable over Naggi in view of Conrad, Appellant maintains that claim 59 is likewise not unpatentable over Naggi in view of Conrad.

GROUND OF REJECTION 5

Claims 1, 43 and 51-54 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, cited in PTO-892) as applied to claims 1 and 56-59 above, and further in view of Kerbel et al. (Cancer and Metastasis Reviews, 2001, 20, p79-86, cited in PTO-892).

Claim 1

With respect to claim 1, the Examiner has not invoked Conrad or Kerbel as a reference as allegedly disclosing any feature specific to claim 1. The Examiner appears to rely on Naggi as allegedly disclosing all of the features of claim 1 based on the Examiner's prior arguments with respect to Naggi allegedly anticipating claim 1 allegedly.

In response, Appellant relies on Appellant's arguments *supra* as to why Naggi does not teach or suggest all of the features of claim 1.

Accordingly, Appellant maintains that claim 1 and is not unpatentable over Naggi in view of Conrad, and further in view of Kerbel.

Claim 43

With respect to claim 43, the Examiner has not invoked Conrad or Kerbel as a reference as allegedly disclosing any feature specific to claim 43. The Examiner appears to rely on Naggi as allegedly disclosing all of the features of claim 43 based on the Examiner's prior arguments with respect to Naggi allegedly anticipating claim 43.

In response, Appellant relies on Appellant's arguments *supra* as to why Naggi does not teach or suggest all of the features of claim 43.

Accordingly, Appellant maintains that claim 43 and is not unpatentable over Naggi in view of Conrad, and further in view of Kerbel.

Claim 51

Since claim 51 depends from claim 43, which Appellant has argued *supra* to not unpatentable over Naggi in view of Conrad, Appellant maintains that claim 51 is likewise not unpatentable over Naggi in view of Conrad, and further in view of Kerbel.

Claim 52

Since claim 52 depends from claim 43, which Appellant has argued *supra* to not unpatentable over Naggi in view of Conrad, Appellant maintains that claim 52 is likewise not unpatentable over Naggi in view of Conrad, and further in view of Kerbel.

Claim 53

Since claim 53 depends from claim 43, which Appellant has argued *supra* to not unpatentable over Naggi in view of Conrad, Appellant maintains that claim 53 is likewise not unpatentable over Naggi in view of Conrad, and further in view of Kerbel.

Claim 54

Since claim 54 depends from claim 43, which Appellant has argued *supra* to not

unpatentable over Naggi in view of Conrad, Appellant maintains that claim 54 is likewise not unpatentable over Naggi in view of Conrad, and further in view of Kerbel.

GROUND OF REJECTION 6

Claims 1, 56, 61 and 62 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, cited in PTO-892) in view of Scholander (US Patent 6,461,665, issued 08 Oct 2002, of record).

Claim 1

With respect to claim 1, the Examiner has not invoked Scholander as a reference as allegedly disclosing any feature specific to claim 1. The Examiner appears to rely on Naggi as allegedly disclosing all of the features of claim 1 based on the Examiner's prior arguments with respect to Naggi allegedly anticipating claim 1.

In response, Appellant relies on Appellant's arguments *supra* as to why Naggi does not teach or suggest all of the features of claim 1.

Accordingly, Appellant maintains that claim 1 and is not unpatentable over Naggi in view of Scholander.

Claim 56

Since claim 56 depends from claim 1, which Appellant has argued *supra* to not unpatentable over Naggi in view of Scholander, Appellant maintains that claim 56 is likewise not unpatentable over Naggi in view of Scholander.

Claim 61

Since claim 61 depends from claim 56, which Appellant has argued *supra* to not

unpatentable over Naggi in view of Scholander, Appellant maintains that claim 61 is likewise not unpatentable over Naggi in view of Scholander.

Claim 62

Since claim 62 depends from claim 56, which Appellant has argued *supra* to not unpatentable over Naggi in view of Scholander, Appellant maintains that claim 62 is likewise not unpatentable over Naggi in view of Scholander.

SUMMARY

In summary, Appellant respectfully requests reversal of the October 27, 2008 Office Action rejection of claims 1, 2, 5-6, 43, 49-54, 56-59, 61-63 and 91-94.

Date: 05/27/2009

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Shaker A. Mousa | Group Art Unit: 1623

Application No.: 10/667,216 | Examiner: Lau, Jonathan S.

Filing Date: 09/19/2003 | Docket No.: **MOUSA-4618**

Title: **OXIDIZED HEPARIN FRACTIONS AND THEIR USE IN INHIBITING ANGIOGENESIS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPENDIX A - CLAIMS ON APPEAL

1. An oxidized heparin fraction having a molecular weight of from about 2,000 to about 4,000 daltons,

wherein the oxidized heparin fraction is super-sulfated such that the super-sulfated oxidized heparin fraction comprises an anticoagulant reduction characteristic and an angiogenesis inhibition characteristic;

wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction;

wherein the super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis.

2. The oxidized heparin fraction of claim 93, wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic.

5. The oxidized heparin fraction of claim 93, wherein the anticoagulant reduction characteristic comprises the second anticoagulant reduction characteristic.

6. The oxidized heparin fraction of claim 93, wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic and the second anticoagulant reduction characteristic.

43. A composition comprising from about 60% to about 100% of the oxidized heparin fraction of claim 1, and from about 0% to about 40% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan sulfates, heparin derivatives, or combinations thereof.

49. The composition of claim 43, further comprising a non-heparin anticoagulant.

50. The composition of claim 49, wherein the non-heparin anticoagulant is selected from the group consisting of anti-Xa compounds, anti-IIa compounds, anti-tissue factor compounds, anti-VIIa compounds, and combinations thereof.

51. The composition of claim 43, further comprising a non-heparin angiogenic inhibitor.

52. The composition of claim 51, wherein the non-heparin angiogenic inhibitor is selected from the group consisting of integrin inhibitory compounds, angiostatin, endostatin, fibroblast growth factor inhibitors, fibroblast growth factor receptor inhibitors, vascular endothelial growth factor inhibitors, thrombospondin, platelet factor 4, interferon, interleukin 12, thalidomide, and combinations thereof.

53. The composition of claim 43, further comprising a cytotoxic or chemotherapeutic agent.

54. The composition of claim 53, wherein the cytotoxic or chemotherapeutic agent is selected from the group consisting of nitrogen mustard, aziridine thiotepa, alkyl sulfonate, nitrosoureas, platinum complexes, non-classic alkylators, substituted urea, antitumor antibiotics, microtubule agents, and asparaginase.

56. A polymeric structure comprising the oxidized heparin fraction of claim 1, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or copolymerization, non-covalently incorporated into a matrix of the polymeric structure, or encapsulated as a biomedical material within the polymeric structure.

57. The polymeric structure of claim 56, wherein said oxidized heparin fraction is non-covalently incorporated into the matrix.

58. The polymeric structure of claim 57, wherein the matrix comprises a biocompatible polymer and provides for a sustained release of said oxidized heparin fraction.

59. The polymeric structure of claim 58, wherein said biocompatible polymer is ethylene vinyl acetate.

61. The polymeric structure of claim 56, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting.

62. The polymeric structure of claim 56, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by copolymerization.

63. The polymeric structure of claim 56, wherein said oxidized heparin fraction is encapsulated as said biomedical material within the polymeric structure.

91. The oxidized heparin fraction of claim 1, wherein the super-sulfated oxidized heparin fraction comprises a sulfate to carboxylate ratio of about 5:1.

92. The oxidized heparin fraction of claim 1, wherein from about 50% to about 100% of primary hydroxyls in glucosamine residues and secondary hydroxyl groups in disaccharide units are substituted by O-sulfate esters in the O-sulfated oxidized heparin fraction.

93. The oxidized heparin fraction of claim 1,

wherein the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof;

wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood;

wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT); and

wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium.

94. A method, comprising forming the oxidized heparin fraction of claim 1, wherein said forming the oxidized heparin fraction comprises O-sulfating the first oxidized heparin fraction by performing sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Shaker A. Mousa

Group Art Unit: 1623

Application No.: 10/667,216

Examiner: Lau, Jonathan S.

Filing Date: 09/19/2003

Docket No.: **MOUSA-4618**

Title: **OXIDIZED HEPARIN FRACTIONS AND THEIR USE IN INHIBITING ANGIOGENESIS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPENDIX B - EVIDENCE

There is no evidence entered by the Examiner and relied upon by Appellants in this appeal.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Shaker A. Mousa | Group Art Unit: 1623

Application No.: 10/667,216 | Examiner: Lau, Jonathan S.

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APPENDIX C - RELATED PROCEEDINGS

There are no proceedings identified in the "Related Appeals and Interferences" section.